Acute Pancreatitis in Scorpion Envenoming Syndrome: Insulin-Glucose Administration Reverses Haemodynamic Changes, Pulmonary Edema and Other Clinical Manifestations Due to Scorpion (Mesobuthus tamulus Concanesis, Pocock [Buthidae family]) Stings

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ABSTRACT

Death due to poisonous scorpion (Buthidae family) stings is a common event in the developing countries. Scorpion envenoming syndrome results in autonomic storm, release of catecholamines, angiotensin II, glucagon, glucocorticoids, either suppressed insulin secretion or hyperinsulinemia; hyperglycemia, lipolysis – sudden increase in free fatty acids (FFA), acute myocarditis, disseminated intravascular coagulation, cardiovascular disturbances, pulmonary oedema, acute pancreatitis, and many clinical manifestations. Under these altered hormonal milieu, insulin administration reversed the metabolic and ECG changes induced by scorpion envenoming in the experimental animals and in scorpion sting victims. Insulin has a primary metabolic role in preventing, counter-acting and reversing the metabolic, cardiovascular, haemodynamic, and neurological manifestations and pulmonary oedema induced by scorpion envenoming and reversing all the deleterious effects of FFA by inhibiting the catecholamine induced lipolysis, and increase intra-cellular K⁺, facilitating glucose transport to the myocardium and glucose metabolism through different pathways. Profuse sweating, excessive salivation and abdominal pain are the triad of symptoms of ominous significance in scorpion sting victims with acute pancreatitis. Laryngeal spasm and respiratory failure are more common with acute pancreatitis. Continuous infusion of regular crystalline insulin should be given at the rate of 0.3 U/g glucose and glucose at the rate of 0.1 g/kg body weight/hour, for 48–72 hours, with supplementation of potassium as needed and maintenance of fluid, electrolytes and acid-base balance.

KEYWORDS: Autonomic storm, Acute myocarditis, DIC, MSOF, Acute pancreatitis, Scorpion, Acute myocarditis

INTRODUCTION

Human envenoming by scorpions is a life-threatening hazard and fatal accidents are common in many regions of the world. It is a rural emergency. Death due to poisonous scorpion stings is common in tropical and subtropical regions. Envenomation by scorpions is an important public health problem especially in the developing countries of the world. More than 70–80 developing countries declared scorpion envenoming as a public health hazard[1–23]. Scorpion stings produce acute myocarditis, hypertension, hypotension, shock, hemi-paresis, pulmonary oedema, many other changes and cause death. We have demonstrated acute myocarditis[13–19], cardiac sarcolemmal defects[13], glycogen depletion in cardiac muscle, skeletal muscles and liver[7,8], hyperglycemia [13–19], disseminated intravascular coagulation (DIC)[22], elevation of Free Fatty Acid levels (FFA)[14–24], reduced insulin secretions[14–16] in the experimental animals with scorpion envenoming syndrome. All these cardiovascular, haemodynamic,
hematological and endocrine alterations could be due to autonomic storm\cite{1–13,15}. Acute pancreatitis has also been reported as one of the causes of death\cite{5,10–12,23}.

Majority of the scorpion venoms contain neuro toxins and cardio toxins. The scorpion venom acts on sodium channels of nerve terminals, cause depolarization and release several neurotransmitters, which affect various systems including gastrointestinal tract, cardio vascular, respiratory and central nervous systems. Kinins, eicosanoids, cytokines, platelet activating factor, permeability increasing factor, nitric oxide and many other mediators affecting inflammatory processes may also be released along with neurotransmitters. These account for several of the inflammatory manifestations observed in Systemic Inflammatory Response Syndrome (SIRS), Adult Respiratory Distress Syndrome (ARDS) leading to pan-systemic injury causing Multi-System-Organ-Failure (MSOF) and death\cite{24,25}.

**Death Due to Scorpion Envenoming from India**

Hundreds of thousands of deaths due to poisonous scorpion stings take place every year in Rayalaseema region of Anantapur, Kurnool and Kadapa districts; Prakasam, Nellore, Ongole and Vijayanagaram districts in Andhra Pradesh\cite{1–4,6–8}; Vellore in Tamilnadu; Bellary in Karnataka\cite{11}; Konkan region in Maharashtra; many districts in Gujarat; Rajasthan; West Bengal; Madhya Pradesh and Uttar Pradesh in India\cite{1–4,6–8,26}.

**Poisonous Species of Scorpions of Buthidae Family from India**


*Titus serrulatus* (yellow scorpion) is a killer scorpion from Brazil\cite{12}. *T. serrulatus*, *T. stigmurus* and *Titus bahiensis* are responsible for most of the accidents in Brazil\cite{10,12}.

Experimental studies have established that Titustoxin, a highly purified fraction of the venom of *T. serrulatus*, acts by activating the sodium channels, causing persistent membrane depolarization in the excitable cells of the organism\cite{12}.
Abdominal pain, nausea, vomiting, diaphoresis, prostration, arterial hypertension, arterial hypotension, restlessness, excessive salivation, hyperglycemia, leucocytosis, amylasemia, pH <7.35 are few of the clinical features in many of the scorpion sting victims[5–11,25].

The experimental basis of the physiological basis of acute pancreatitis in scorpion envenoming syndrome and its reversal (in the experimental animals and scorpion sting victims) by administration of insulin are reviewed.

**Autonomic Storm**

Our experimental animals after envenomation exhibited lacrimal secretions with profuse salivation. The saliva was thick and ropy in nature. Some of these animals passed watery stools, often stained with bile and blood, and had simultaneous urination. These behavioural changes indicate the autonomic storm.

**Larger Doses of Venom Injection Result in Release of Greater Amounts of Catecholamines**

Larger doses of venom injection result in release of greater amounts of catecholamines. This in turn causes cardiogenic shock and vasoconstriction severe enough to produce tissue destruction and thereby less depletion of tissue glycogen content from atria, ventricles; liver and skeletal muscles. This may be the reason for non-uniformity in the histo-pathological findings and abnormalities observed in coagulation studies reported by different workers[7–12,20,21,27].

**Metabolic Actions of Catecholamines in Scorpion Envenoming Syndrome**

As catecholamines released during autonomic storm have been responsible for glycogenolysis[7,8], hyperglycemia, lipolysis[14–16,19–22,28], a reduction in H+ ion concentration in gastric secretion[29,30] also will take place with scorpion envenomation. The H+ ion concentration in gastric secretion was reduced significantly in the venom-injected animals. Reduction (80%) in gastric H+ ion concentration was observed within 30–40 min after envenoming[29].

Hemorrhagic necrosis of the intestinal mucosa, mucosal edema and congestion in the stomach were observed[22,29].

**Reduced H+ Ion in Gastric Acid Secretion Due to Nor-epinephrine**

Acid secretion is controlled by autonomic nervous system, hormones and blood flow to the gastric mucosa. Adrenergic neuro-humoral transmitters such as Nor-epinephrine may exert some inhibitory action on gastric acid secretion indirectly through limiting mucosal blood flow[31]. This could be one of the factors for the reduced H+ ion concentration.

**Changes in the Blood Sugar is An Important Regulatory Mechanism for Gastric Acid Secretion**

Changes in the blood sugar are another important regulatory mechanism for gastric acid secretion. Venom treated dogs and rabbits showed acute hyperglycemia[7,8,15–22,27,28,30]. Blood sugar increased from 100 mg/100 ml (fasting) to 320 mg/100 ml (sometimes exceeding 800 mg/100 ml[15–22,27,28,30].

Rise in the blood sugar could be as a consequence of release of catecholamines after scorpion envenomation. The catecholamines in turn cause suppression of insulin secretion resulting in hyperglycemia and reduced gastric acid secretion[13–15,20,22,32].

**Non-cholinergic and Nor-adrenergic Fibers in the Vagus Inhibit Gastric Acid Secretion**

Non-cholinergic and Nor-adrenergic fibres in the vagus nerve when stimulated inhibit gastric acid secretion. In this mechanism, sympathetic nerves and intrinsic plexuses also play a role. This could be the reason for reduction of gastric acid secretions as manifested by sinus arrest in the animals treated with scorpion venom.
Increased Gastrin Levels and Gastric Juice Volume

Gastrin levels were increased 15 min after toxin injection. Partly purified T₁ fraction from Tityus serrulatus scorpion venom given intravenously in rats increased gastric juice volume fourteen times. This occurred 40 min after toxin injection. The mechanism of toxin-induced Gastrin release might be dependent on gastric vagal nerve ending stimulation since scorpion toxin acts through the stimulation of nerve endings. Vagal stimulation is important for Gastrin release in the rat stomach, which occurs by cholinergic (acetylcholine) and non-cholinergic mechanisms such as bombesin. The Gastrin releasing factor is important for Gastrin release in humans. Since scorpion toxin releases acetylcholine from post-ganglionic nerve endings and histamine from enterochromaffin-like cells, it may be possible that bombesin and other peptides could also be released. All these substances can stimulate G-cells with consequent increase in serum Gastrin levels.

The clinical manifestations could vary depending upon whether there was more Para-sympathetic stimulation or sympathetic stimulation. The release of either sympahtetic adrenergic neuro transmitters or cholinergic neuro transmitters depends upon the concentration of the scorpion venom. This could be the reason for an increase in Gastrin stimulated gastric acid secretion observed by Toppa et al.[31] and inhibition of gastric acid secretion reported by Radha Krishna Murthy et al.[33].

Gastric distension is another important factor in Gastrin release.

Gastric distension is another important factor in Gastrin release by cholinergic mechanism[28]. Distension of abdomen is a frequent observation due to envenoming by Mesobuthus tamulus Concanensis, Pocock[7–23].

Labeled Venom Acts on Pancreas but Retention May not Occur in Pancreas

We have demonstrated labelling, biodistribution and scintiimaging using 99m Tc-scorpion venom. This study showed that uptake of venom by different organs. In vitro studies using scorpion venom of different species demonstrated that the venom has toxic effects on heart, stomach, pancreas, lungs and various organs, which may account for myocarditis, changes in gastric secretion, acute pancreatitis, pulmonary oedema and many other clinical manifestations, respectively. The level of the labelled venom (0.32%) at 5 min) dropped to 0.05% after 4 h, indicating that the clearance of Tc 99m scorpion venom from the pancreas was very fast[28,34].

Acute Pancreatitis: Increase in Serum Amylase Levels – Hyperglycemia, Leucocytosis

All scorpion sting victims had elevated serum amylase levels, leucocytosis, increased blood glucose values, glucosuria, and an increase in CK, CK-MB and Total LD, LD₁ >LD₂ was observed in all the patients reported by Hering[12]. Bucaretchi et al. observed “amylasemia” >180 U/dl, hyperglycemia, leukocyte count (range 10,100–37,400 mm³), increase in CK-MB (Creatine kinase isoenzyme MB) (range 8.5–68.6 U/dl), CK (Creatine kinase enzyme activity) (range 29–693 U/dl)[10].

Increased serum amylase levels were reported by Bucaretchi et al. in 12 out of 12 children with scorpion envenoming syndrome caused by Tityus serrulatus (5). Hering et al. reported increased serum amylase levels in 11 out of 14 scorpion sting children. Increase in amylase was observed in scorpion sting victims from Brazil[10, 12, 35]. Amaral et al. reported an increase in serum amylase, leucocytosis (range 12,900–31,980 mm³), hyperglycemia, CK (Creatine kinase enzyme); CK-MB (Creatine kinase isoenzyme MB), VPC (Ventricular Premature complexes), Myocardial infarction like pattern; pulmonary oedema in their patients[36].

Acute Pancreatitis: Signs and Symptoms in Scorpion Sting Victims

Abdominal pain, local pain, nausea/vomiting, sialorrhea,
lacrimation, profuse sweating, tachydispnoea, precordial pain, arrhythmias, hypertension, agitation, tremors, hypothermia, priapism, increased amylase, hyperglycemia, leucocytosis, elevated levels of AST (aspartate aminotransferase), CK, CK-MB, LD (Lactic Dehydrogenase), LD₃, LD₂ (Lactic dehydrogenase isoenzymes) were reported from scorpion sting patients[12].

There was an increase in Amylase and lipase levels (18) in the blood within 30–40 min after administration of the venom[33]. These levels continued to remain high 16–18 hours after venom injection. The amylase activity rises within 2–12 hours of the onset of symptoms.

However, as a diagnostic test, estimation of Amylase has many drawbacks. It is not specific as there are many other causes of hyper-amylasemia. Moreover, raised activity has no prognostic significance. The serum amylase levels remains normal in 10% of the cases of lethal pancreatitis.

**Acute Pancreatitis: Increased Serum Lipase levels**

Serum lipase activity is probably more specific to pancreatic disease than amylase. 60% of the rabbits treated with scorpion venom exhibited an elevated lipase activity whereas only 20% of these had a parallel increase in amylase. Only 50% of the scorpion (Mesobuthus tamalus concanesis, Pocock) venom poisoned dogs showed an elevation of amylase as well as lipase whereas 3 out of 12 dogs showed an elevated amylase more with lipase (more than 1 unit)[29]. However, all these animals showed consistent rise in lipase levels. These results from our experimental animals are suggestive of acute pancreatitis[29].

**Scorpion Venom Acts Directly on the Pancreas to Cause Increased Exocrine Output with an Outflow Obstruction**

Tityus serrulatus venom stimulates pancreatic exocrine secretion associated with a rise in serum amylase[5]. Bartholomew suggested that the scorpion venom acts directly on the pancreas to cause increased exocrine output with an outflow obstruction[5].

**Acute Pancreatitis has a Wide Gamut of Manifestations**

Acute Pancreatitis has a wide gamut of manifestations and often the diagnosis is not considered.

**Problem with Differential Diagnosis of Abdominal Pain**

Most patients with Acute Pancreatitis seen by the clinician present a problem with differential diagnosis of abdominal pain. If the pain happens to be rather mild and tolerable, the patient is likely to be dismissed as having psychological symptoms[11].

**Acute Pancreatitis May be Fulminant and Rapidly Fatal**

The disease Acute Pancreatitis may be fulminant and rapidly fatal. Bartholomew reported that 53% patients had profuse salivation with abdominal pain (3). This confirms that acute pancreatitis may occur more often than is realized. Moreover, the severity of the abdominal pain did not correspond to the level of hyper-amylasemia.

**Triad of Symptoms of Ominous Significance**

Profuse sweating, excessive salivation and abdominal pain are the triad of symptoms of ominous significance in scorpion sting victims[11].

**Laryngeal spasm and respiratory failure are more common with acute pancreatitis**

Hyperglycemia[9,14–22,30,32], hypocalcemia[22] and disseminated intravascular coagulation[20] have been demonstrated in the experimental dogs. Release of Trypsin activates plasminogen and this can lead to disseminated intravascular coagulation[22].

The experimental animals also showed muscle fasciculations, clonus and tetany like muscular spasms.
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Hypocalcemia and hyperkalemia are few of biochemical abnormalities. The venom poisoned animals also had laryngeal spasm[3] and respiratory failure. These are much more with acute pancreatitis [20,22,29,32,33].

It is suggested that all scorpion sting victims with hypersalivation and abdominal pain should be observed for acute pancreatitis.

**Diagnosis of Acute Pancreatitis – Serum Amylase**

The diagnosis of acute pancreatitis is usually established by the detection of increased levels of serum amylase. Values threefold or more above normal clinch the diagnosis.

**No correlation Between the Severity of Pancreatitis and Serum Amylase Elevation**

There appears to be no definite correlation between the severity of pancreatitis and the degree of serum amylase elevation. After 48–72 hours, even with continuing evidence of pancreatitis, total serum amylase values tend to return to normal. However, pancreatic isoamylase and lipase levels may remain elevated for 7–14 days.

**Acidemia (Arterial pH<7.32) May have Spurious Elevations in Serum Amylase**

Patients with acidemia (arterial pH<7.32) may have spurious elevations in serum amylase. Patients with diabetic ketoacidosis may have marked elevations in serum amylase without any other evidence of acute pancreatitis[37]. An elevated serum lipase or Trypsin value is usually diagnostic of acute pancreatitis.

**Leucocytosis**

Leucocytosis (15,000–20,000 mm³) occurs frequently in acute pancreatitis. Patients with severe acute pancreatitis may show Hemoconcentration with hematocrit values exceeding 50% because of loss of plasma into retroperitoneal space. We have demonstrated leucocytosis in our experimental animals[15,16].

**Hyperglycemia**

Hyperglycemia is common and could be due to[1–4] decreased insulin release[14–16,27,28,32,33,38], increased glucagon release[15, 16], an increased output of adrenal glucocorticoids[15,16] and catecholamines [37]. We have demonstrated hyperglycemia in our experimental animals. We have also reported (1) suppressed insulin secretion, (2) increased glucagon release and (3) an increased output of adrenal glucocorticoids in our experimental animals.

**Hypocalcemia**

Hypocalcemia occurs in approximately 25% of patients. It was thought earlier that the response of the parathyroid gland to a decrease in serum calcium is impaired. Intraperitoneal saponification of calcium by fatty acids in areas of fat necrosis occurs occasionally, with large amounts (up to 6.0 g) dissolved or suspended in ascetic fluid. Such “soap formation” may also be significant in patients with pancreatitis and mild hypocalcemia[37]. We have demonstrated hypocalcemia in our experimental animals.

**Hyperbilirubinemia**

Hyperbilirubinemia (serum bilirubin >68 μmol/L (>4.0 mg/dL) may occur. Increased frequency of passing of urine, defecation and the stools were stained with blood and bile in our experimental animals after scorpion envenoming.

**Elevated Serum Alkaline Phosphatase and Aspartate Aminotransferase**

Serum alkaline Phosphatase and aspartate aminotransferase (AST) levels are elevated[37]. We have demonstrated elevated Serum alkaline Phosphatase and aspartate aminotransferase levels in our experimental animals.

**Elevated Serum Lactic Dehydrogenase**

Elevated serum lactic dehydrogenase takes place in acute pancreatitis (33). We have demonstrated
elevated serum lactic dehydrogenase levels in our experimental animals.

**Decreased serum albumin**

Decreased serum albumin takes place in acute pancreatitis[37]. Ismail et al. demonstrated decreased serum albumin levels in their experimental animals.

**Hypoxemia (arterial $P_{O_2} < 60$ mmHg)**

60–80% of scorpion sting victims develop hypoxemia (arterial $P_{O_2} < 60$ mmHg) and develop pulmonary oedema and ARDS[37]. We have demonstrated hypoxemia (arterial $P_{O_2} < 60$ mmHg) in our experimental animals.

**Electrocardiogram**

ECG is abnormal in acute pancreatitis with ST-segment and T-wave abnormalities simulating myocardial ischemia[26,30,37,32,39]. We have demonstrated abnormal ECG changes with ST-segment and T-wave abnormalities simulating myocardial ischemia in our experimental animals.

**Risk factors that adversely affect survival in acute pancreatitis**

1. Multi-System-Organ-Failure (MSOF)
   - (a) Cardiovascular: hypotension (systolic blood pressure $< 90$ mm Hg).
   - (b) Tachycardia $> 130$ beats/min
   - (c) Renal; Oliguria ($< 50$ ml/hour)
   - (d) Increasing blood urea nitrogen
   - (e) Increasing creatinine
   - (f) Gastrointestinal building
   - (g) Hemoconcentration (Hematocrit $> 44\%$)
   - (h) Hyperglycemia
   - (i) Hypocalcemia
   - (j) Hypoxemia
   - (k) ARDS

**CONCLUSION**

The metabolic disturbances, ECG changes and cardiovascular manifestations produced by scorpion venom toxicity could be due to

1. Action of catecholamines causing increased myocardial oxygen consumption due to positive and chronotropic effects, coronary vasoconstriction, peripheral vasoconstriction and increased afterload, Lipolysis resulting in increased FFA;
2. Action of angiotensin II resulting in coronary and peripheral vasoconstriction, potentiation of catecholamine mediated effects,
3. Insulin deficiency.
4. Increased Free Fatty Acid levels (FFA) due to the actions of catecholamines, glucagon, glucocorticoid secretions and insulin deficiency seen in scorpion envenoming[15,16].
5. Increased FFA resulting increased myocardial oxygen consumption; and
6. Arrhythmogenic effect of catecholamines, angiotensin II and free fatty acids.

Insulin administration resulted in glycogenesis, lipogenesis, stopped arrhythmias and reversed the ECG changes to sinus rhythm.

**The Dose of Insulin**

All scorpion sting victims with hyper-salivation and abdominal pain should be observed for acute pancreatitis. In addition to the routine management due to acute pancreatitis, all the scorpion sting victims should be given insulin-glucose infusion. The dose of insulin is 0.3 Units of regular insulin per gram of glucose, and glucose 0.1 g kg per hour. Blood glucose, serum electrolytes, electrolydiagram, and arterial blood gases should be investigated on admission. In addition to regular clinical observations, estimations of blood glucose should be carried out two hourly and of serum electrolytes 12-hourly. Glucose levels should be maintained between 130 and 180 mg dl$^{-1}$ of blood.
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